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Short Communication

Norepinephrine and dopamine Imbalance in the medial frontal gyrus from patients with Alzheimer's disease

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ABSTRACT

Objective: To investigate catecholaminergic alterations in the medial frontal gyrus (MFG) in Alzheimer's disease (AD) patients, including a case with TDP-43 pathology, with a focus on norepinephrine (NE) and dopamine (DA) signaling.
Methods: Postmortem MFG tissue from five human donors, one with AD, one with AD and TDP-43 co-pathology (AD-TDP43), one preclinical AD, and two controls, was analyzed using high-performance liquid chromatography. Concentrations of NE, DA, and their primary metabolites (MHPG, DOPAC, HVA) were measured to assess neurotransmitter levels and turnover ratios.
Results: Elevated MHPG levels were observed only in AD and AD-TDP43 patients, despite unchanged NE concentrations, indicating increased NE turnover. DA levels were also selectively elevated in AD and AD-TDP43 brains only. Possible impaired DA metabolism appeared consistent with reduced DOPAC/DA and HVA/DA ratios and DA turnover.
Conclusions: Catecholaminergic dysfunction, marked by increased NE turnover and elevated DA levels, characterizes both AD and AD-TDP43 pathology in the MFG, implicating catecholamine imbalance in disease mechanisms.
Significance: By revealing a selective increase in NE turnover and DA levels in the medial frontal lobe, these data may help to clarify the neurochemical imbalance linking cortical to subcortical neurodegeneration, such as that of the locus coeruleus and ventral tegmental area, to catecholamine innervation of the frontal cortex.

1. Introduction

Alzheimer's disease (AD) is a leading cause of disability and caregiver dependence in older individuals, a fatal neurodegenerative condition marked by memory loss, cognitive decline, and neuropsychiatric symptoms, with two key neuropathological features: accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) formed by hyperphosphorylated tau protein. Evidence suggests that Aβ buildup starts decades before symptoms, though its exact role in proteostasis and synaptic toxicity remains unclear. Similarly, tau hyperphosphorylation is linked to widespread neuron death, but its causal relationship with the disease is debated (Maggiore et al., 2024; Saggu et al., 2024). Furthermore, AD pathology can overlap with other lesions, including cerebrovascular pathology, Lewy bodies, hippocampal sclerosis, and

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aggregation of misfolded TAR DNA-binding protein 43 (TDP43), which can shape the clinical trajectory and severity of dementia symptoms (McAleese et al., 2017). Under pathological conditions, TDP-43 becomes phosphorylated, cleaved, mislocalized to the cytoplasm, and aggregates into inclusion bodies, such as neuronal cytoplasmic inclusions and dystrophic neurites (Meneses et al., 2021). TDP-43 pathology is present in a relevant proportion of AD cases, ranging from approximately 30 % to about 70 %, depending on the cohort and methods of detection (McAleese et al., 2017; Uchino et al., 2015).

Beyond these clinical aspects and neuropathological features, catecholaminergic system dysfunction, including loss of norepinephrine (NE) and dopamine (DA) neurons and disrupted signaling and metabolites (De Paolis et al., 2025; Gannon et al., 2015; Nobili et al., 2017; Zhang et al., 2025), can play a causal role in both cognitive decline and psychiatric manifestations in AD (Pan et al., 2020), including when TDP-43 pathology is studied in association to AD (Loganathan et al., 2022; Pintus et al., 2018). However, while much is learned about cholinergic and DA deficits in AD (De Paolis et al., 2025; Gannon et al., 2015; Nobili et al., 2017; Zhang et al., 2025), there is still a gap in our current knowledge about the balance between NE and DA signaling, particularly in the frontal cortex. A potential imbalance in NE and DA signaling not only may contribute to cognitive impairment but is also closely associated with psychiatric symptoms such as apathy and agitation (Saggu et al., 2024). Studies involving postmortem brain tissue from individuals with AD and imaging studies have shown a significant degeneration of locus coeruleus (LC) neurons (Beardmore et al., 2021; Gannon et al., 2015). Additionally, the degeneration of the LC correlates with the severity of cognitive decline in AD patients, supporting its central role in the disease's progression (Kelly et al., 2017). In parallel, different computational and preclinical models of AD (Caligiore et al., 2020; Nobili et al., 2017) suggest that degeneration of catecholaminergic neurons, such as DA in the ventral tegmental area (VTA), can lead to system-level adjustments in catecholamine release. These changes may trigger events leading to clinical manifestations relevant to AD, highlighting the vulnerability of DA and NE in the disease (Leanza et al., 2018; Szot et al., 2007). The frontal cortex, a region essential for executive function and attention, is particularly susceptible to catecholaminergic dysregulation (Arnsten and Pliszka, 2011). Either reductions or increased levels of DA and NE have been reported in this region, as well as conflicting data reporting the altered activity of metabolic enzymes such as monoamine oxidase and catechol-O-methyltransferase (COMT), 3-Methoxy-4-hydroxyphenylglycol (MHPG) or homovanillic acid (HVA) (Emilsson et al., 2002; Kennedy et al., 2003; Vermeiren et al., 2014).

The present study sought to elucidate alterations in DA, NE, and their metabolite levels (i.e., MHPG, HVA, and DOPAC) in the medial frontal gyrus (MFG) from AD patients. By characterizing these neurochemical changes, this work aims to provide a deeper understanding of NE and DA alterations to AD neuropathology and suggest potential targets for drug development and intervention.

2. Materials and methods

2.1. Subjects

All experiments were performed using postmortem MFG samples from patients and control (CTRL) subjects. The MFG brain samples were obtained from the Cliniques Universitaires Saint-Luc biobank. Tissue micropunches were specifically sampled from the anterior portion of the MFG, corresponding to Brodmann Area 10 (BA10), located within the anterior prefrontal cortex. Sampling was performed at a consistent rostro-caudal level across all cases. To ensure anatomical precision, gray matter was selectively dissected and carefully isolated from any visible white matter prior to downstream biochemical analyses. As diagnostic criteria we used the ABC classification, and specifically, "A" for amyloid pathology assessed using Thal phases (0–5), "B" for Braak staging of regional Tau pathology extension (0–6), and "C" for Cerad assessment of neuritic plaques (0–3). Within this context, the ATN framework (i.e, Amyloid Tau and Neurodegeneration) framework proposed by Clifford and colleagues (Jack et al., 2016) as a biomarker-based descriptive classification was applicable and not used. The samples included cortical grey matter from one AD patient at Braak stage 6 (AD), one patient at Braak stage 2 (pre-AD), and one AD patient at Braak stage 1 with TDP43 pathology (AD-TDP43). All samples were stored frozen in Eppendorf tubes. Braak staging was confirmed through histopathological reports based on the severity of tau pathology. The patient UCL003 with Braak stage 2, whose tau pathology was observed in brain regions such as the entorhinal cortex and hippocampus (different from the frontal cortex), and Thal phase with Aβ-deposition mostly in the allocortex, was used as an internal "healthy" control. Neither the AD patients UCL001 (Braak stage 6) and UCL014 (Braak stage 1) nor the pre-AD patient UCL003 (Braak stage 2) had a family history of AD. Table 1 illustrates demographic information and illness scores. AD patients (i.e., UCL001 and UCL014, see Table 1) are CERAD score = C3, while cognitively intact patient (i.e., UCL003) is CERAD = C2. Control (CTRL) samples were obtained from two non-demented donors, with samples coming both from 90-year-old brains. Ethical approval was granted under committee numbers UCL-2020-355 (Cliniques Universitaires Saint-Luc) and 139/2022 (CHU UCL Namur, Mont-Godinne Hospital). The following Table 1 reports some critical information such as sex, Braak stage and Thal phase, post-mortem interval (PMI), pas medications, pH, neuropathology co-morbidities and RNA Integrity Number (RIN) scores. RIN values in the range of 8–10 are generally indicative of highly preserved RNA quality and are considered suitable for the majority of molecular and transcriptomic research applications.

2.2. HPLC catecholamine and metabolites determination

Tissue levels of NE, DA, and their metabolites were determined by high-performance liquid chromatography with electrochemical detection (HPLC-ECD). The HPLC-ECD system consisted of a pump and column oven (PerkinElmer) inside which a 150-mm Atlantis C18 column (Waters) was inserted at a temperature of 35 °C. The column was connected to an ESA Coulochem II detector equipped with 2 cells, a conditioning cell set at + 350 mV and a detection cell set at − 150 mV (E1) and + 220 mV (E2). The buffer consisting of 0.1 M Na phosphate, 0.1 mM NA2EDTA, and 1-octane sulfonic acid salt of Na 1.78 mM (Sigma) was adjusted to pH 3.0 with 85 % orthophosphoric acid after adding 6 % methanol. The flow rate was set at 1 ml/min. On the days of analysis, micropunches of MFG brain tissue samples frozen at − 80° were weighed and homogenized in an assay buffer consisting of bidistilled water with antioxidant solution (AOX). For each subject, two separate and independent micropunches of MFG tissue were made, thus obtaining N = 6 samples from AD patients (N = 2 AD, N = 2 pre-AD and N = 2 AD-TDP43), and N = 4 samples from the non-demented CTRL subjects. The AOX included 100 mM acetic acid, 3.3 mM L-cysteine, 0.27 μM Na2EDTA, and 12.5 μM ascorbic acid. The assay buffer contained four parts water and one part AOX. For each mg of tissue, 50 microliters of assay buffer were added. The homogenates were centrifuged at 10,000 × *g* for 20 min at 4°. Aliquots of the 30 microliters of supernatant were transferred to the HPLC-ECD system for analysis.

2.3. Statistics

Statistical analyses were carried out on raw data and performed via the GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA. All data are expressed by the mean ± standard error. The level of significance was set at $P < 0.05$. The assumption of normality was assessed by the Shapiro-Wilk test. Two-way analysis of variance (ANOVA) was used to compare differences in NE and DA outflow, and in NE (i.e., MHPG) and DA metabolites (i.e., DOPAC and HVA) in AD, AD-TDP43, Braak 2 subject (pre-AD), and CTRL subjects.

Table 1
Summary of patients with clinical information and different criteria of illness scores.

Patient	Age	Sex	Braak Stage	Thal Phase	Diagnosis	Approx PMI	Past Medications	pH	Neuropathology co-morbidities	RIN score
UCL001	79	male	Braak stage 6	Thal phase 5	AD	24 h	Rivastigmine stopped 10 months before death. No antipsychotic medications	6.7	No co-morbidities	8.6
UCL003	80	male	Braak stage 2	Thal phase 2	Pre-AD cognitively normal	24 h	Antihypertensive drugs, and statins. No antipsychotic medications	6.8	Hypertensive heart disease, dyslipidemia	9
UCL014	74	female	Braak stage 1	Thal phase 3	AD-TDP43 co-pathology	24 h	Rivastigmine (Exelon patch 9.5 mg/24 h) stopped 10 months before death. No antipsychotic medications	6.8	No co-morbidities	8.1

Individual between-group comparisons were carried out by post hoc test (Tukey HSD test). Comparison between the MHPG/NE ratio, DOPAC/DA ratio, and HVA/DA ratio between two groups (CTRL subjects and AD and AD-TDP43 patients) was performed by separate *t*-tests for independent samples. Effect sizes was assessed by eta squared calculation (η^2) and Cohen's *d* for ANOVA and *t*-test, respectively.

3. Results

No significant effects for NE tissue levels between AD and AD-TDP43 patients, Pre-AD subject, and CTRL subjects were found ($F_{3,6} = 3.11$, $p = 0.18$) ns ($\eta^2 = 0.64$) (Fig. 1/A). Significant effects for DA tissue levels between AD and AD-TDP43 patients, Pre-AD subjects, and CTRL subjects were found ($F_{3,6} = 20.84$) $p < 0.0001$, ($\eta^2 = 0.94$) (Fig. 1/B). Post-hoc analysis (Tukey HSD) revealed that DA tissue levels were significantly higher in AD and AD-TDP43 patients than in CTRL and Pre-AD subjects (Fig. 1/B). Significant effects for the NE metabolite MHPG were found ($F_{3,6} = 18.45$) $p < 0.0001$, ($\eta^2 = 0.92$) (Fig. 1/C). Post-hoc analysis revealed that MHPG levels were significantly higher in AD and AD-TDP43 patients than in CTRL and Pre-AD subjects (Fig. 1/C). No significant effects for the DA metabolite DOPAC between AD and AD-TDP43 patients, Pre-AD subject, and CTRL subjects were found ($F_{3,6} = 2.48$, $p = 0.23$) ns ($\eta^2 = 0.28$) (Fig. 1/D). Similarly, no significant effect for the DA metabolite HVA between AD and AD-TDP43 patients, Pre-AD subject, and CTRL subjects were found ($F_{3,6} = 1.08$, $p = 0.47$) ns ($\eta^2 = 0.46$) (Fig. 1/E). The MHPG/NE ratio in the group of AD and AD-TDP43 patients was significantly higher than in the group of CTRL subjects $t = 12.33$ (df 3), $p < 0.001$ (Cohen's $d = 4.21$) (Fig. 1/F). The DOPAC/DA ratio in the group of AD and AD-TDP43 patients was significantly lower than in the group of CTRL subjects $t = 4.36$ (df 3), $p < 0.005$ (Cohen's $d = 2.79$) (Fig. 1/G). The HVA/DA ratio in the group of AD and AD-TDP43 patients was significantly lower than in the group of CTRL subjects $t = 10.35$ (df 3), $p < 0.005$ (Cohen's $d = 3.44$) (Fig. 1/H). * $p < 0.005$; ** $p < 0.01$.

4. Discussion

The present study shows evidence focused on relevant alterations in catecholaminergic signaling found within the MFG of the frontal lobe in patients with AD and AD-TDP43 co-pathology. Specifically, we detected in both AD patients an increase in NE turnover without corresponding changes in NE tissue levels, suggesting an enhanced NE turnover potentially compensating for neuronal dysfunction and degeneration in this region. This finding aligns with prior research linking NE turnover and NE signaling to neuroprotection against neuroinflammation (Evans et al., 2024), a fundamental hallmark of neurodegeneration and AD pathology.

Moreover, enhanced NE turnover (i.e., elevated MHPG/NE ratio) has been associated with reduced cortical thickness and hippocampal volume (van Hooren et al., 2021) and possible consequence of LC degeneration and loss of the primary source of NE, leading to a compensatory increase in NE turnover in surviving neurons that overcompensate to maintain neurotransmission. In this view, the NE system may become overactivated with increased NE breakdown as a defensive mechanism against chronic neuroinflammation, oxidative stress, and microglial activation. However, an elevated MHPG/NE ratio can also correlate with advanced stages of disease. Thus, the increased MHPG/NE ratio may reflect the reduced ability to maintain homeostasis in the face of progressive LC degeneration and NE depletion. Interestingly, there is evidence that the NE system in the prefrontal cortex plays a critical role in regulating both cognitive and non-cognitive processes (Amsten and Simon, 2000; Friedman and Robbins, 2021). Deviations from optimal NE levels, whether through depletion or excessive release, can disrupt high-level executive functions such as attention and working memory (Ramos and Arnsten, 2007). This is supported by primate studies showing that pharmacological activation of α_1-adrenoceptors, as well as heightened NE signaling in the dorsolateral prefrontal cortex, impairs working memory performance (Birnbaum et al., 2004).

Additionally, we detected a marked elevation in DA tissue levels in the same MFG region of both AD and AD-TDP43 patients, but not in the Pre-AD patient or healthy controls. This selective increase may indicate dysregulated dopaminergic activity associated with neurodegenerative pathology (Pan et al., 2019). Cognitive and executive functions operates through different frontal-subcortical circuits such as dorsolateral prefrontal, orbitofrontal, and anterior cingulate (Tekin and Cummings, 2002). Dopaminergic and NE signaling within the frontostriatal system play an essential role for regulating executive functions as established for attention-deficit/hyperactivity disorder (Del Campo et al., 2011). Dysfunctional dopamine signaling in the MFG may contribute to hyperexcitability and prefrontal network disruption, impairing cognitive flexibility and working memory (Granon et al., 2000). Such circuit-level disruptions are consistent with the neurobiology of psychosis and may underlie the exacerbation of neuropsychiatric symptoms observed in AD (Maggiore et al., 2024). One interpretation is that the increase of DA may reflect a compensatory neurochemical response to cortical dysfunction, potentially triggered by reduced cholinergic input. This is supported by the well-documented decline in acetylcholine (ACh) levels in AD and the complex, reciprocal interaction between ACh modulation and DA release and function (Cao et al., 2005; Kosillo et al., 2016). The tight DA-ACh functional relationship is, for instance, corroborated by the observation that the increase of DA input in patients with AD can modify the cholinergic cortical excitability (Martorana et al., 2009). Otherwise, the increase in DA levels may represent a neuropathological dopaminergic imbalance across cortical and subcortical circuits that contributes to disease progression. The dysregulation of the DA system could also be linked to AD-associated systemic inflammation or microglial activation and upregulation of enzymatic activity, and in particular, of tyrosine hydroxylase activity, leading to excessive DA accumulation (Chakrabarti and Bisaglia, 2023; He et al., 2020). In lack of proper vesicular storage (e.g., via VMAT2), cytosolic DA becomes susceptible to degradation by monoamine oxidase and to spontaneous auto-oxidation. These processes generate reactive oxygen species and toxic quinones, significantly contributing to oxidative stress and neuronal damage (Hastings, 2009; Meiser et al., 2013). Excessive DA synthesis can produce neurotoxic species secondary to DA oxidation, such as reactive DA quinones and ROS, leading to neuronal loss (Meiser

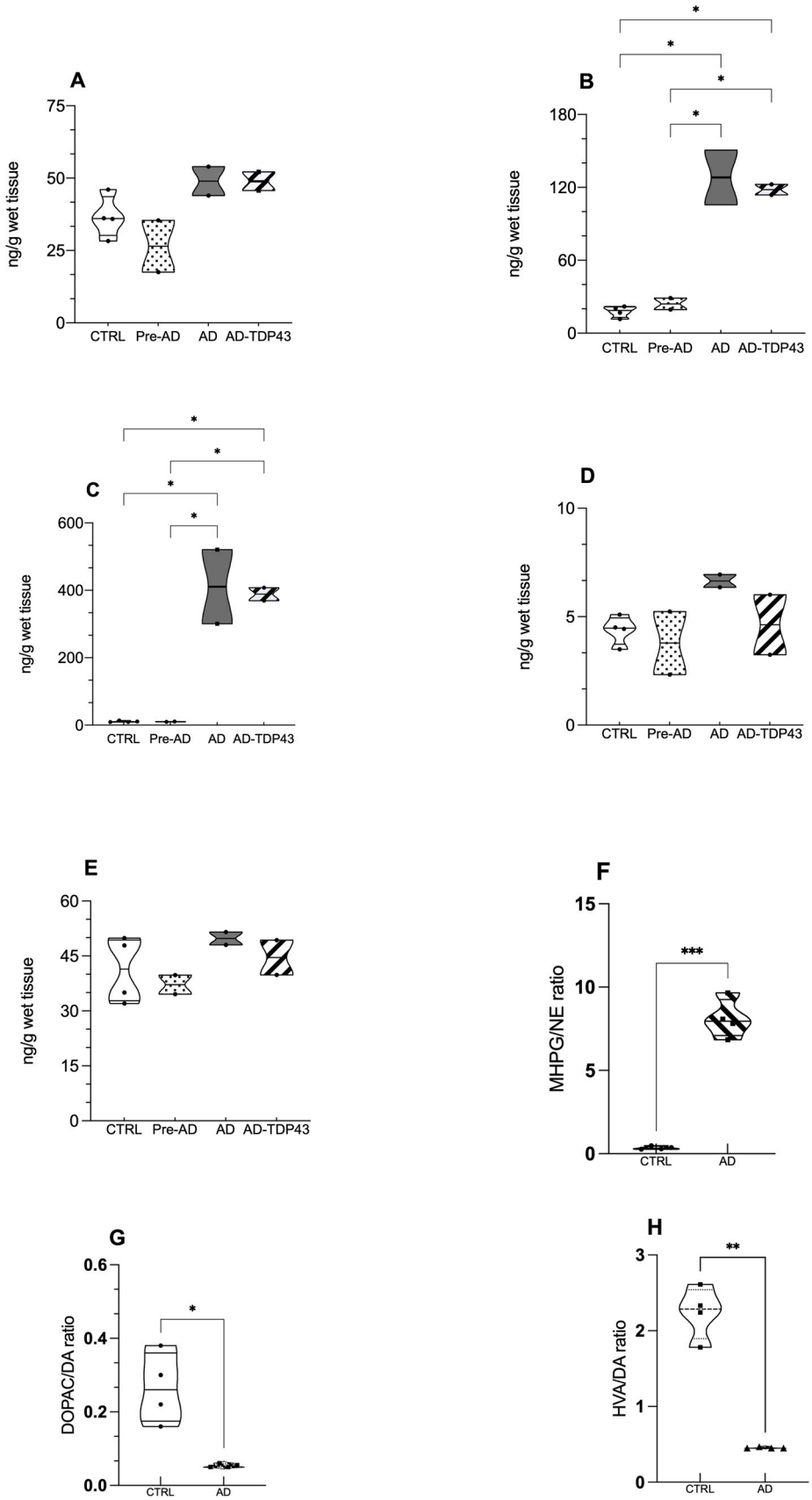

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Fig. 1. A) NA levels (ng/g) in CTRL subjects (N=4), Pre-AD (N=2), AD (N=2), and AD-TDP43 (N=2) patients; B) DA levels (ng/g) in CTRL subjects (N=4), Pre-AD (N=2), AD (N=2), and AD-TDP43 (N=2) patients; C) MHPG levels (ng/g) in CTRL subjects (N=4), Pre-AD (N=2), AD (N=2), and AD-TDP43 (N=2) patients; D) DOPAC levels (ng/g) in CTRL subjects (N=4), Pre-AD (N=2), AD (N=2), and AD-TDP43 (N=2) patients; E) HVA levels (ng/g) in CTRL subjects (N=4), Pre-AD (N=2), AD (N=2), and AD-TDP43 (N=2) patients; F) MHPG/NE turnover ratio in CTRL subjects (N=4) and AD patients (N=4); G) DOPAC/DA turnover ratio in CTRL subjects (N=4) and AD patients (N=4); H) HVA/DA turnover ratio in CTRL subjects (N=4) and AD patients (N=4). *$p<0.005$; **$p<0.01$.

et al., 2013). On the other hand, the increase of DA levels in the MFG could also be a response to the loss of VTA neurons and, therefore, to the loss of mesencephalic DA neurons. Reduced numbers of DA neurons in the VTA, or reduced dopaminergic VTA activity, have been observed in AD patients and in AD-like mouse models (Nobili et al., 2017; Zhang et al., 2025). Early degeneration of VTA neurons could disrupt DA projections to cortical areas, forcing compensatory mechanisms. Thus, in response to the loss of VTA neurons, the neural network may attempt to compensate by increasing DA signaling in the cortex. In parallel, a loss of DA neurons in the nigrostriatal pathway has been described in FTLD (Murley and Rowe, 2018). These potential compensatory mechanisms align with the hypothesis of upregulated TH activity in intact dopaminergic pathways, such as the mesocortical projections, and impaired reuptake of DA resulting from dysfunction in cortical DA and NE transporters (DAT and NET). Together, these changes may prolong DA signaling duration in an attempt to maintain dopaminergic homeostasis. Moreover, a possible increase of sprouting or activity of remaining dopaminergic terminals in the MFG, and thus enhanced plasticity of DA terminals, is an additional non-mutually exclusive mechanism that could amplify DA release in response to VTA neuron loss. There is also compelling evidence that the prefrontal cortex can directly control the mesolimbic DA signaling via the reciprocal modulation of NE and DA transmission (Pascucci et al., 2007). During exposure to unavoidable and uncontrollable stress, there is an increase in NE outflow in the prefrontal cortex and DA release in the ventral striatum. Over time, in case of persistent stress, such changes in catecholamine levels were found to be replaced by the enhancement of prefrontal cortex release of DA and by a decrease of DA outflow in the ventral striatum.

Lastly, both DOPAC/DA and HVA/DA ratios were reduced in AD and AD-TDP43 patients. DOPAC/DA and HVA/DA ratios serve as indices of DA turnover and may provide valuable insights into the status and activity of dopaminergic fibers innervating the MFG. DOPAC and HVA are products of distinct DA degradation pathways: monoamine oxidase B (MAO-B) converts DA to DOPAC, while catechol-O-methyltransferase (COMT) allows the conversion of DOPAC to HVA or 3-methoxytyramine (3-MT) to HVA via MAO-B. Interestingly, mechanisms of DA clearance may vary across different brain regions within the mesocorticolimbic system. Although COMT and the DA transporter (DAT) both contribute to DA removal from the synaptic cleft, their regional distribution differs significantly. DAT is predominantly expressed in the striatum, whereas COMT is more abundant in the prefrontal cortex (Weinberger et al., 2001) where it plays a crucial role in DA metabolism. In this context, the observed decrease in the HVA/DA ratio in AD patients may be attributed to COMT downregulation in the MFG. This downregulation could, in turn, contribute to the increased DA concentration detected in the same brain region. The higher expression of COMT in the prefrontal cortex (Matsumoto et al., 2003) is thought to support cognitive functions such as executive functioning (e.g., working memory) and cognitive flexibility, both of which are notably impaired in AD patients. The critical role of the COMT-dependent pathway in regulating DA levels in the prefrontal cortex is further supported by findings that inhibition of NET, rather than DAT inhibition, leads to a significant increase in DA content, an effect that is further amplified by *Comt* gene deletion (Käenmäki et al., 2010). According to this study, COMT activity accounts for approximately 50 % of DA clearance and metabolism in the prefrontal cortex. Although speculative, COMT downregulation in the MFG of AD patients may underlie both the observed increase in DA levels and the reduction in the HVA-to-DA ratio.

This study provides evidence of significant alterations in catecholaminergic signaling within the MFG of AD and AD-TDP43 patients, highlighting both potential compensatory mechanisms and dysfunctional neurochemical responses. The observed increase in NE turnover, without a corresponding rise in NE levels, suggests an attempt to preserve neurotransmission amid neuronal dysfunction and LC degeneration. While this compensatory elevation in NE metabolism may initially exert neuroprotective effects, it could become maladaptive as disease progression may impair homeostatic regulation. Concurrently, the marked increase in DA levels within the MFG of these patients indicates a region-specific dysregulation of DA activity. This imbalance may emerge as a compensatory response to broader neurotransmitter deficits, such as mesolimbic and nigrostriatal DA depletion, or as a result of altered enzymatic activity. However, excessive DA accumulation and heightened DA signaling could also contribute to cognitive decline, oxidative stress, synaptic dysfunction, and the neuropsychiatric disorders frequently observed in AD (Maggiore et al., 2024). Additionally, the reduced HVA/DA ratio suggests a potential downregulation of COMT, further amplifying DA accumulation and potentially exacerbating cognitive impairments.

5. Conclusions and limitations

This study demonstrates pronounced catecholaminergic alterations in the MFG of patients with AD and AD-TDP43 co-pathology, characterized by increased NE turnover and elevated DA levels accompanied by reduced DA turnover. These findings suggest a complex interplay between compensatory and maladaptive mechanisms that may contribute to cortical dysfunction and disease progression. Increased NE turnover in the absence of elevated NE levels may suggest compensatory hyperactivity within the locus coeruleus-frontal projection system, whereas elevated DA levels with reduced turnover ratios imply possible disrupted DA metabolism, potentially related to COMT downregulation or vesicular storage deficits. Although limited by the small number of cases, the consistent neurochemical patterns observed across AD and AD-TDP43 samples support the view that catecholaminergic dysregulation represents a shared cortical signature in neurodegenerative pathology. Nevertheless, interpretation is constrained by the lack of longitudinal data, and the inability to directly correlate neurochemical findings with clinical measures. Despite these limitations, these findings underscore that catecholaminergic imbalance in the medial frontal cortex may not only mark disease progression but also represent a potential target for therapeutic modulation of NE and DA signaling in AD. The potential influence of postmortem and clinical confounders on catecholaminergic measurements was carefully evaluated. All three donors exhibited brain pH values within the acceptable range for tissue quality and postmortem biochemical analyses (6.7–6.8), minimizing the likelihood of pH-related catecholamine degradation (Monoranu et al., 2009). Postmortem intervals were consistent with intervals not known to significantly alter monoamine or metabolite levels when tissue is appropriately stored and processed (Kontur et al., 1994). Both AD and AD-TDP43 patients had discontinued rivastigmine therapy approximately ten months before death, and none had received antipsychotic or dopaminergic agents capable of influencing NE or DA metabolism. The pre-AD subject received only antihypertensive and lipid-lowering medications, which do not affect cortical catecholamine levels. Furthermore, no neuropathological comorbidities were present in the AD or AD-TDP43 cases, and the pre-AD subject showed only systemic vascular conditions without brain involvement. Together, these factors indicate that the observed differences in NE turnover and DA metabolism are

unlikely to reflect confounding effects of pH, postmortem interval, medication history, or comorbid pathology. Future studies integrating biochemical, imaging, and clinical approaches will be essential to clarify whether restoring catecholamine homeostasis can mitigate cognitive and neuropsychiatric symptoms in AD.

CRediT authorship contribution statement

Emanuele Claudio Latagliata: Methodology, Investigation, Data curation. **Giovanni Augusto Carlesimo:** Funding acquisition. **Roberto Coccurello:** Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Silvia Capuani:** Project administration, Formal analysis. **Zuleyha Nihan Yurtsever:** Investigation. **Charles Nicaise:** Resources, Investigation. **Michela Fratini:** Resources, Project administration. **Bernard Hanseeuw:** Resources, Methodology. **Yasmine Salman:** Resources.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Ethical approval was granted under committee numbers UCL-2020-355 (Cliniques Universitaires Saint-Luc) and 139/2022 (CHU UCL Namur, Mont-Godinne Hospital).

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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